Updating the probability of study success for combination therapies using related combination study data

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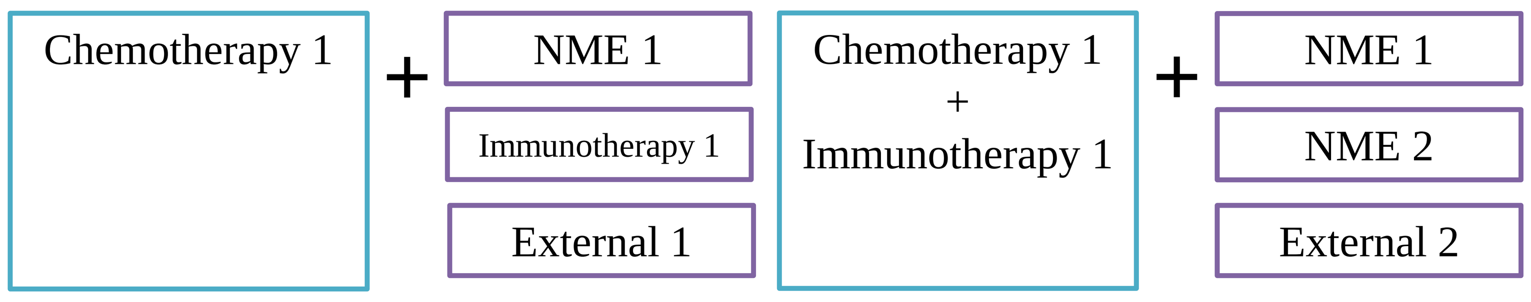
Introduction

- **Combination therapies** are becoming increasingly used, especially in areas such as oncology.
- In 2017, there were over **10000 clinical trials** containing combinations ongoing in the US.
- **Relationships** may exist between combinations which have at least one treatment in common.
- We can update the **probability of success** (PoS) of a combination study using related study data.



Method

- Let $\boldsymbol{\theta} = (\theta_1, \theta_2)^T$ represent the treatment effects of two related combinations with prior distribution

$$\boldsymbol{\theta} \sim \text{MVN}\left(\boldsymbol{\mu}, \boldsymbol{\Sigma}\right).$$

- We summarise the outcome of a study on θ_2 using the score statistic, Z_2, and Fisher's information, V_2.

$$Z_2 \mid \theta_2 \dot{\sim} \text{N}\left(V_2\theta_2, V_2\right)$$

- Using the conditional properties of **Gaussian Markov Random Fields**, we can update our multivariate prior given our univariate likelihood.

$$\boldsymbol{\theta}|Z_2 \sim \text{MVN}\left(\boldsymbol{\mu}^{\text{post}}, \boldsymbol{\Sigma}^{\text{post}}\right)$$

- We can calculate our **updated PoS** for a study on θ_1 using

$$\text{PoS} = 1 - \Phi\left(\frac{V_1^{-0.5}Z_{\alpha/2} - \mu_1^{\text{post}}}{\sqrt{V_1^{-1} + \sigma_1^{2\text{post}}}}\right).$$

Robustification

- We can use a **mixture prior** to robustify against the possibility that θ_1 and θ_2 may not be correlated.

$$\boldsymbol{\theta} \sim w_0 \cdot \text{MVN}\left(\boldsymbol{\mu}, \text{diag}\left(\boldsymbol{\Sigma}\right)\right) + w_1 \cdot \text{MVN}\left(\boldsymbol{\mu}, \boldsymbol{\Sigma}\right)$$

- We can update the individual distributions as above.
- The **weights** can be updated using

$$w_0' = \frac{(1-p)w_0}{(1-p)w_0 + pw_1} \qquad w_0' + w_1' = 1$$

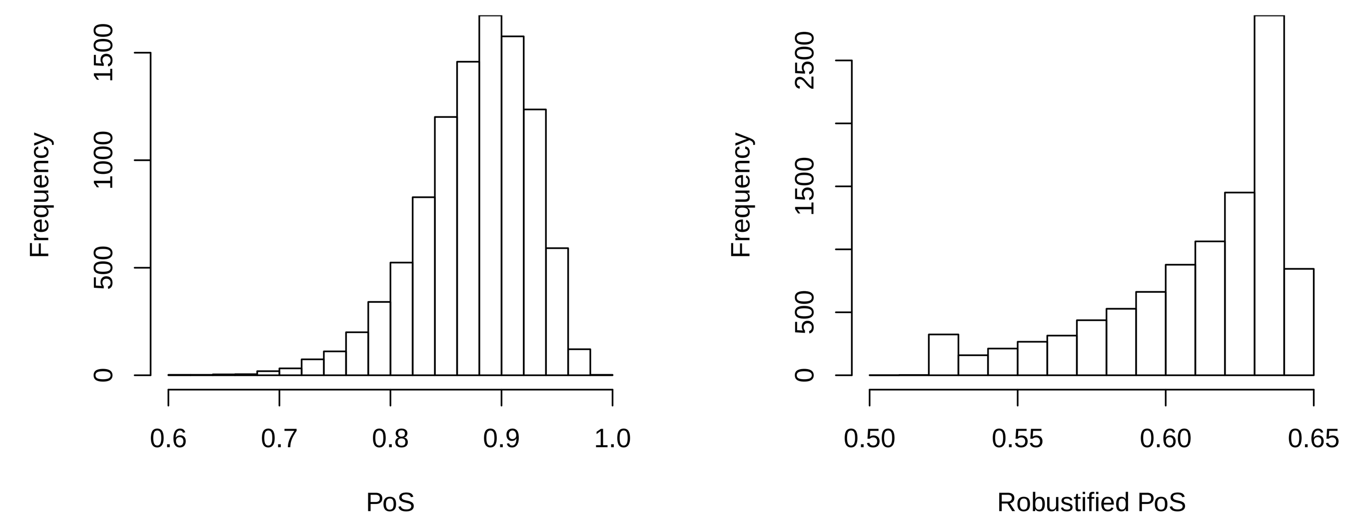
where p is defined to capture how much of the observed data we would wish to borrow.

Results

- Let us assume a prior distribution of

$$\begin{pmatrix}\theta_1\\ \theta_2\end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix}0.2\\ 0.2\end{pmatrix}, \begin{pmatrix}0.2 & 0.16\\ 0.16 & 0.2\end{pmatrix}\right).$$

- We will observe a study on θ_2 with $V_2 = 125$.
- We are interested in a similar study on θ_1.
- The prior PoS for the study on θ_1 is 0.5202.
- Using 10000 simulations of Z_2 where the true value of θ_2 was set to 0.5, the mean posterior PoS:
  - is 0.8204 using the standard procedure;
  - is 0.6102 using the robustified approach when p is defined to consider $|\mu_1^{\text{post}} - \mu_1|$ and V_2.

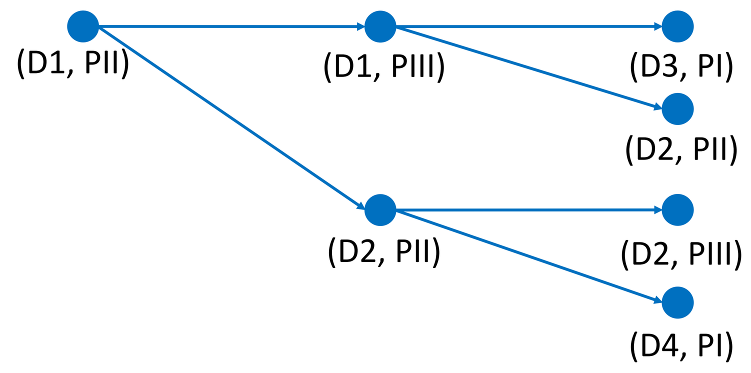


Discussion

- This method can be generalised for n combinations.
- It allows the PoS to be updated each time a **relevant outcome** is observed.
- It could be applied in different settings e.g. the same combination in **different indications**.

Further Work

- Several methods exist for **portfolio management** which use stochastic programming.
- These methods treat **single agent** and **combination** drug development similarly.



- The approach presented here can be incorporated into the existing methods.
- This will allow potential outcomes and **related studies** to be considered in the **planning** process.

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